

### **REMARKS**

Claims 1-13, 15-23 and 25-33 constitute the pending claims in the present application. Claims 1, 11, 13, 15-23, and 28-32 are under consideration having been elected with traverse.

Applicants have amended claim 1. Support for amended claim 1 can be found throughout the specification, particularly at page 4, lines 16-20, page 24, lines 25-30 and Figure 1. Applicants respectfully submit that amended claim 1 does not add any new matter to the application.

Applicants have cancelled claim 29 without prejudice and reserve the right to add the subject matter of this claim to an application claiming priority to the instant application.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

#### **Claim rejections under 35 USC §112, first paragraph**

Claims 28-32 are rejected under 35 U.S.C. §112, first paragraph as lacking enablement. Specifically, the Office Action states that one skilled in the art would not accept the data presented in the specification obtained from neural cells cultured *in vitro* as reasonably correlating to a pharmaceutical preparation. The Examiner cites to a publication that allegedly “teaches that cultures . . . cannot offer unequivocal prediction for responses of adult neurons.” (Office Action, p. 3, citing to Hefti et al., *J. Neurobiology* 25(11):1418-35 (1994) (“Hefti”).)

Applicants respectfully traverse the Examiner’s rejection. Applicants submit that using cultured neural cells *in vitro* to determine survival of mammalian neural cells is a proper model that reasonably correlates with the effect of the *in vivo* administration of morphogens and neurotrophic factors. Hefti only states that cell culture does not offer unequivocal prediction for responses of adult neurons. However, “[a] rigorous or an invariable exact correlation is not required.” See MPEP § 2164.02. See also *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). Thus, the fact that *in vitro* cultures do not offer unequivocal prediction for responses of adult neurons does not indicate that the model does not provide the required correlation to support a claim for an *in vivo* method.

Further, Applicants submit herewith a publication that shows that OP-1 (BMP-7) enhances the *in vivo* survival of spinal cord motor neurons (See Exhibit 1, Granholm et al., “Effects of Osteogenic Protein-1 (OP-1) Treatment on Fetal Spinal Cord Transplants to the

Anterior Chamber of the Eye,” *Cell Transplantation* 8:75-85, 77-78 (1999) (“Granholm”). Further, published articles show that GDNF also enhances the *in vivo* survival of motor neurons. See Manabe et al., “Glial Cell Line-Derived Neurotrophic Factor Protein Prevents Motor Neuron Loss of Transgenic Model Mice for Amyotrophic Lateral Sclerosis,” *Neurological Research* 25:195-200 (2003) (Exhibit 2) (“Our study indicates that the GDNF treatment prevented motor neuron loss through preserving survival signaling . . .”). See also Granholm (“We have previously shown that GDNF, when injected directly into the intraocular fluid . . . can enhance survival of spinal cord tissue transplanted to the anterior chamber of the eye.”)

In view of the fact that: (1) morphogens such as OP-1 have been shown to enhance the survival of neurons *in vitro* and *in vivo*, (2) GDNF or NGF neurotrophic factors have also been shown to enhance the survival of neurons *in vitro* and *in vivo*, and (3) a morphogen and a GDNF or NGF neurotrophic have been shown to have a synergistic effect on the survival of neurons *in vitro*, a person of skill in the art would reasonably expect to observe this synergistic effect when these factors are co-administered *in vivo*. Thus, in this case, the *in vitro* model disclosed in the specification reasonably correlates to the expected *in vivo* results. MPEP § 2164.02 states that even if the Examiner presents evidence that a particular model does not correlate to a specific condition, “the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition.”

Further, while the Examiner acknowledges that the specification teaches fiber outgrowth and survival in ganglia cultures *in vitro*, the Examiner argues that the experiments disclosed in the specification fail to disclose whether inhibition of death or degeneration occurred in a cell. Without acknowledging to the correctness of the Examiner’s remarks, and in order to expedite the prosecution of the instant claims, Applicants have cancelled claim 29 without prejudice.

In view of the above arguments, Applicants respectfully request the Examiner to reconsider its rejection of claims 28-32 under 35 USC §112, first paragraph.

Claims 1, 13, and 15-23 are also rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. The Examiner argues that the specification is enabling for a method for promoting survival of mammalian peripheral ganglia *in vitro*. The Examiner cites to references that allegedly state that the effects of OP-1 and NT-5 are cell specific. Specifically, the Examiner cites to Lein *et al.*, *Int. J. Devl. Neuroscience* 14(3):203-215 (1996) (“Lein”) which

allegedly states that OP-1 does not promote dendritic growth in cultured neurons obtained from embryonic ciliary, dorsal root, trigeminal or nodose ganglia. The Examiner also cites to Berkemeier *et al.*, *Neuron* (1991) which allegedly teaches that NT-5 promotes the survival or sympathetic ganglion neurons but does not promote the survival or peripheral sensory nodose ganglion neurons.

The applicants respectfully traverse the Examiner's objection. The instant application teaches that morphogen combined with neurotrophic factor enhances the survival of peripheral neuron cells (PNS neurons). Applicants submit that there is no intrinsic difference between PNS neurons and CNS neurons. Applicants are submitting herewith a copy of a publication that demonstrates that the co-administration of a morphogen (BMP-2) and a neurotrophic factor (e.g., NT-3 and GDNF) enhances the survival of CNS neurons *in vitro*. See Reiriz et al., "BMP-2 and cAMP Elevation Confer Locus Coeruleus Neurons Responsiveness to Multiple Neurotrophic Factors," *J. Neurobiol.* 50(4):291-304 (2002) (Exhibit 3) ("In the presence of BMP-2, GDNF or NTN increased the number of TH-positive neurons by 118%, NT-3 by 164%, and bFGF by 97%, compared to the corresponding factors in the absence of BMP-2."). Thus, the evidence as a whole shows that the claimed combination of morphogen and neurotrophic factors enhance the survival of PNS and CNS neurons.

Accordingly, in Applicants' view, the scope of the present claims fully satisfies the enablement requirement of 35 U.S.C. 112, first paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections under 35 USC §103(a)

Claims 1, 11, 13 and 15-23 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Lein in view of Trupp *et al.*, *J. Cell Biol.* (1995) ("Trupp"). Specifically, the Examiner contends that Lein teaches that OP-1 induces dendritic growth, and that Trupp teaches that GDNF promotes the survival of embryonic chick sympathetic neurons, embryonic chick nodose ganglion and embryonic sensory neurons. The Examiner states that "[t]he motivation and expected success is provided by Lein et al. who demonstrates the importance of OP-1 in the regulation of cytoskeletal structures of neural cells which would be important for cell signaling and maintenance." Also, the Examiner states that "[o]ne would be motivated to use OP-1 because dendritic growth would positively affect neural survival."

It is well established that it is the burden of the PTO to establish a *prima facie* case of obviousness of the invention as a whole for a rejection under 35 U.S.C. §103. *See* MPEP §2143. When relying on a combination of two or more references to establish a *prima facie* case of obviousness, the PTO must show that there is some suggestion or motivation to combine the prior art references. This suggestion or motivation can be found in the prior art references themselves, in the knowledge generally available to one skilled in the art or, in some cases, from the nature of the problem to be solved. This showing must be clear and particular. “Broad conclusory statements regarding the teaching of multiple references, standing alone, are not ‘evidence.’” *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999), *abrogated on other grounds*.

The Examiner’s argument that a skilled artisan would be motivated to combine the teachings of Lein and Trupp is completely unsupported. Lein does not disclose or suggest that OP-1 could be used to promote cell survival. Further, Lein does not suggest or disclose administering GDNF in addition to OP-1. Moreover, nothing in Trupp discloses or suggests administering a morphogen in combination with GDNF to promote survival of neural cells.

The Examiner states that “one would be motivated to use OP-1 because dendritic growth would positively affect neural survival.” However, Lein states that “OP-1 . . . promotes the extension of dendrites without affecting cell survival.” (*See* Lein, p. 12, emphasis added.) In view of this statement, Applicants respectfully submit that a person of skill in the art would not be motivated to combine the teachings of Lein and Trupp to arrive at the claimed invention.

Further, in order to establish a *prima facie* case of obviousness a reasonable expectation of success is required. In this case, a person of skill in the art would not have expected that the administration of OP/BMP morphogens and GDNF/NGF neurotrophic factors would show a synergistic effect when used in the claimed methods. Claims 1, 11, 13 and 15-33 have been amended to recite that the OP/BMP morphogen and the GDNF/NGF neurotrophic factor act synergistically to promote survival of mammalian neural cells as taught by the instant application. *See, e.g.*, application, page 4, lines 16-20, page 22, lines 25-30 and Figure 1. Figure 1 shows that OP-1 and NT-3 act synergistically so that treatment with OP-1 and NT-3 results in increase survival as compared to treatment with OP-1 alone or NT-3 alone, or when compared to the additive effects of treatment with OP-1 alone and NT-3 alone. (Figure 1 also shows that OP-1 and GDNF also act synergistically as described above with respect to OP-1 and NT-3.)


Nothing in either Trupp or Lein teaches or suggests that OP/BMP morphogen and the GDNF neurotrophic factor or NGF neurotrophic factor act synergistically to promote survival of mammalian neural cells. Therefore, applicants respectfully submit that even if Lein and Trupp were combined, a person of ordinary skill in the art would have had no reasonable expectation of success in obtaining the methods of amended claims 1, 11, 13 and 15-33. Based on the argument presented above, Applicants submit that claims 1, 11, 13 and 15-33 are not obvious over the cited references.

### CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. The Examiner may address any questions raised by this submission to the undersigned at 212-497-3624. Applicants believe that no fee, other than the fee for the three-month extension of time, is due at this time. If there are any other fees due in connection with the filing of this submission, please charge the fees to Deposit Account No. 18-1945.

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Respectfully submitted,

By  \_\_\_\_\_  
Gloria Fuentes  
Registration No.: 47,580  
ROPES & GRAY LLP  
45 Rockefeller Plaza  
New York, NY 10111  
(212) 497-3624  
(212) 497-3650 (Fax)  
Attorney For Applicants